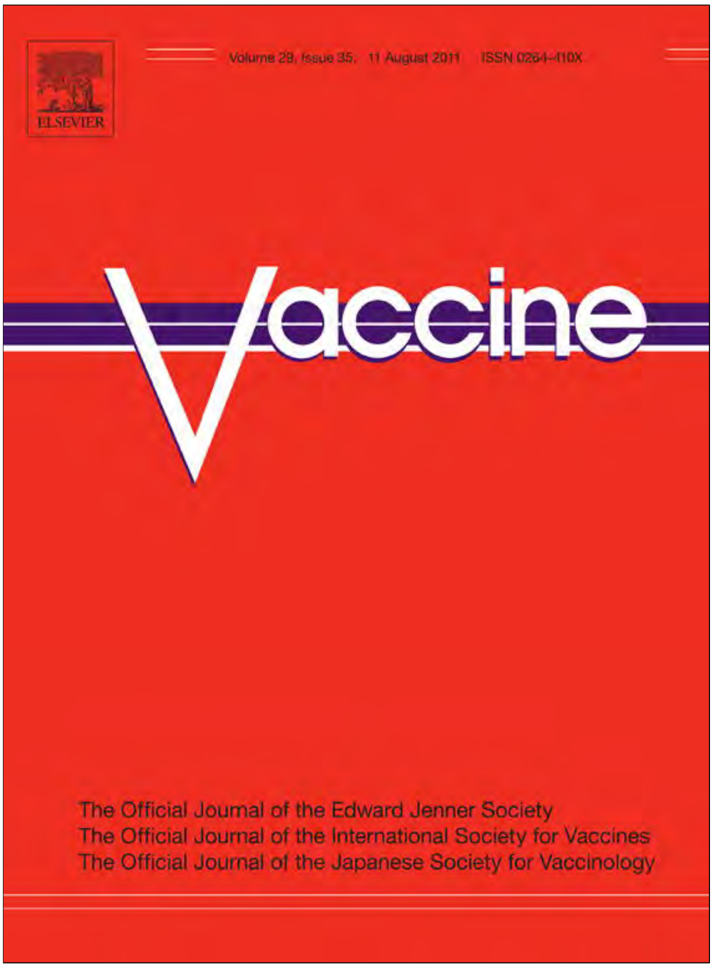
Volume 29, Issue 35, 11 August 2011 ISSN 0264-410X
ELSEVIER
Vaccine
The Official Journal of the Edward Jenner Society
The Official Journal of the International Society for Vaccines
The Official Journal of the Japanese Society for Vaccinology

Report Documentation Page

Form Approved
OMB No. 0704-0188

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1. REPORT DATE **JUN 2011**	2. REPORT TYPE	3. DATES COVERED **00-00-2011 to 00-00-2011**

4. TITLE AND SUBTITLE **Risk of disability for US army personnel vaccinated against anthrax, 1998-2005**	5a. CONTRACT NUMBER 5b. GRANT NUMBER 5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER 5e. TASK NUMBER 5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Office of the Surgeon General of the Army,Military Vaccine Agency,Falls Church,VA,22041**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S) 11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
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15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**8**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

Vaccine 29 (2011) 6035–6041

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Risk of disability for US army personnel vaccinated against anthrax, 1998–2005☆

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ARTICLE INFO

Article history:
Received 11 March 2011
Received in revised form 3 June 2011
Accepted 9 June 2011
Available online 23 June 2011

Keywords:
Anthrax vaccine
Disability
Army

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To evaluate the potential for long-term or delayed onset health effects, we extended a previous cohort study of disability separation from the army associated with vaccination against anthrax. Analyses included stratified Cox proportional hazards and multiple logistic regression models. Forty-one percent of 1,001,546 soldiers received at least one anthrax vaccination; 5.21% were evaluated for disability. No consistent patterns or statistically significant differences in risk of disability evaluation, disability determination, or reason for disability were associated with anthrax vaccination. There was a dose-related trend in risk of disability for soldiers with 2 years' service, limited to those entering service in 2000 or later. Divergent patterns in risk suggest confounding by temporal or occupational risks of disability.

1. Introduction

The Department of Defense has concluded that threats to US troops posed by biological weapons containing anthrax spores are real, and vaccination with anthrax vaccine adsorbed (AVA) provides effective protection against anthrax infection [1–3]. The Anthrax Vaccine Immunization Program was initiated in March 1998; over time, different groups of US military personnel were given high priority for vaccination. By September 2008, >8.3 million doses of anthrax vaccine had been administered to >2.2 million individuals.

Previous studies addressed shorter- and longer-term health adverse effects (AE) and reproductive outcomes [4–14]. Reported short-term adverse effects were similar to those resulting from other adult vaccines in severity, frequency and gender distribution [15–17]. No published study has produced evidence of increased risk of any lasting condition associated with AVA. Limitations of previous studies include incomplete control of confounders; self-reported exposure and health outcomes; and inadequate power and/or duration of follow-up [4,6–11,13,18]. This report updates a cohort study of delayed onset or long-term health effects associated with AVA [14]. The original analysis revealed no association between vaccination and risk of disability evaluation or separation from the army among 716,833 Active Component Army personnel followed between December 1997 and February 2002 [14], but may be limited by its relatively short length of follow-up (average 3.2 years, standard deviation (SD) 1.5 years).

2. Methods

All US Army personnel active between December 15, 1997 and February 15, 2005 were eligible study cohort members. Data were from the Total Army Injury and Health Outcomes Database (TAIHOD), which links data from sources including the Defense Manpower Data Center (DMDC) and the Army Physical Disability Agency (PDA) [19]. Anthrax vaccination data were obtained from the Military Vaccine (MILVAX) Agency (Table 1). The protocol for this study was reviewed and approved by the Institutional Review Boards of ENVIRON International Corporation, the Army Research Institute of Environmental Medicine, and the Army Medical Research and Materiel Command.

For each eligible soldier, we abstracted the earliest data available from up to 18 semi-annual DMDC updates. We retained the earliest and latest recorded calendar dates of entry into and separation from Service, respectively. For 585,881 soldiers with no recorded separation date, we calculated a date three months from the last DMDC file that indicated active service. Records of hostile fire pay (HFP) were used to detect combat deployment.

We defined outcomes from the first recorded disability evaluation that did not result in return to duty, categorized as severance with or without benefits; temporary or permanent disability discharge; and non-traumatic cause of disability. Using these data, we identified soldiers as ever/never evaluated for disability, as well as according to the type of disability categorized using the Veterans Administration Schedule for Rating Disabilities (VASRD):

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doi:10.1016/j.vaccine.2011.06.028

Table 1
Descriptions and source of analysis variables.

Group	Variable	Source
Occupational/Demographic	Age at entry into service	DMDC
	Age at beginning of follow-up	DMDC
	Race/ethnicity	DMDC
	Duration of service	DMDC
	Major command code	DMDC
	Pay grade (categorized) at beginning of follow-up	DMDC
	Hostile fire pay indicator	PAY
	Ever stationed abroad	DMDC
	Ever stationed in Southwest Asia	DMDC
	Ever stationed in South Korea	DMDC
Administrative	Pay entry base date	DMDC
	Date of separation from Army	DMDC/LOSS
	Duration of follow-up	DMDC
Vaccination	Received ≥1 dose AVA	MILVAX
	Total number doses AVA	MILVAX
	Date of first dose AVA	MILVAX
	Rank at first dose AVA	MILVAX
	Vaccine lot number	MILVAX
Disability	Disability evaluation date	USAPDA
	Disposition	USAPDA
	Category of VASRD (primary disability)	USAPDA

musculoskeletal, neurological, respiratory, mental, digestive, cardiac, endocrine and other. One of us (PJA) categorized musculoskeletal disabilities as due to traumatic or non-traumatic causes based on clinical experience and familiarity with army coding systems, and our a priori assumption that there is no plausible connection between anthrax vaccination and traumatic injury. The primary analyses focused on the broadest definition (ever/never evaluated for disability). Additional analyses investigating the association between vaccination against anthrax and the more detailed categories of outcomes are provided in Supplementary Tables.

Start of follow-up was the latest of entry into service or the start of the study (December 15, 1997). Follow-up ended at the earliest of: separation from service, earliest disability evaluation, or end of study (February 1, 2005). Duration of follow-up was time from start to end of follow-up.

From MILVAX data, we abstracted anthrax vaccination dates, total doses delivered, and vaccine lot numbers. Exposed soldiers received ≥one dose of AVA during the study period, and were further categorized according to numbers of doses received.

Soldiers who entered Active Duty after the study ended (February 1, 2005) and those who left service or received their first dose of AVA before the study started (December 15, 1997) were excluded from analysis. If the earliest available disability record was coded "Retained on Temporary Disability List (TDRL)," we considered it likely that an earlier record was missing; data for these individuals were excluded. We excluded soldiers whose data appeared unreliable based on age at entry into service ≤16 years and those appearing to have <1-day of follow-up. All soldiers were required to have completed at least three months Active Duty service to avoid analyzing disabilities due to injury sustained during Basic Combat Training (BCT). Anthrax vaccinations are not delivered during BCT.

2.1. Statistical methods

We used chi-squared tests to compare prevalence of vaccination and disability evaluation, respectively, across occupational and demographic categories to identify potential confounders, and then developed Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals (CI) to describe the risk of disability outcomes associated with vaccination status. The Cox models provided statistical significance tests of the effect of vaccination on risk of disability.

Preliminary log–log plots indicated the proportional hazards assumption underlying the Cox model was badly violated for duration of service; we therefore stratified all models by mutually exclusive categories of duration of service [20,21]. Bivariate analyses additionally indicated that vaccination status varied strongly by sex and race, known predictors of disability in the army [22], so we adjusted for these factors. Initial models describing the effect of vaccination on risk of disability outcomes were unsatisfactory due to inconsistent, uninterpretable increases and decreases in risk across categories of individual covariates. We therefore developed core models that included the strongest predictors of disability outcomes (i.e., demographic and occupational variables), and tested whether or not vaccination contributed meaningfully to the model. This is analogous to the approach used for clinical trials of treatment effects requiring control for confounding due to baseline differences between treatment groups [23]. Variables were retained in the core model according to the amount of variability they explained (likelihood scoring) and if their inclusion resulted in ≥15% change in the other HRs [23]. We calculated percent change in risk of disability due to vaccination as $(HR_{\text{core model}}) - (HR_{\text{core model}} + HR_{\text{core+vaccine indicator}})/(HR_{\text{core model}})$ [24], and used the partial log likelihood ratio test to assess the contribution of the vaccine indicator to the model. For brevity, and because gender was the strongest predictor of disability evaluation, tables and figures in this report only describe the incremental risk due to vaccination for women compared to men, stratified by categories of duration of service. Analyses of the incremental effect of vaccination on risk of disability in other stratified models are shown in Supplementary Tables.

The majority of the cohort had neither been vaccinated against AVA nor evaluated for disability, so there were too few observations within risk sets to use Cox models to assess dose-response relationships. Thus, we used multiple logistic regression models to investigate whether odds of disability evaluation increased with more doses of AVA.

3. Results

The 18 DMDC files provided data for 1,188,037 soldiers on active duty at any time between December 15, 1997, and February 1, 2005. We excluded data for 56,867 soldiers whose service start dates were after the end of the study and 77,218 who ended army service prior to the study start date. Records for 3037 subjects were excluded because they had been vaccinated before the study began; 2669 were excluded because their recorded age at entry to service was less than 16 or greater than 35 years, which are likely to be inaccurate values. Data for 918 subjects were dropped because their duration of service or follow-up appeared to be 1 day or less. Subjects whose records indicated vaccination or disability after the end of the study remained in the cohort but had their vaccination or disability indicators set to zero. Reasons for exclusion were not mutually exclusive; after all exclusions, the cohort consisted of 1,001,546 soldiers, 43.8% (439,059) of whom had received at least one dose of AVA (Table 2).

As shown in Table 2, vaccination history was relatively uniform across demographic groups, including race/ethnicity, age at start of follow-up, educational attainment and marital status, except that men were more likely than women to have been vaccinated (46% vs. 34%). In contrast, there was substantial variability in vaccination history according to occupational covariates: senior enlisted personnel (grades E7–E9) were less likely to be vaccinated

Table 2
Distribution of occupational/demographic factors by anthrax vaccination status (n = 1,001,546).

Occupational/demographic factor	# Vaccinated (%)	Total
Gender		
Male	383,300 (45.7)	838,391
Female	55,759 (34.2)	163,155
Race/ethnicity		
White	264,233 (42.5)	621,213
Black	104,443 (45.6)	229,001
Hispanic	42,951 (47.4)	90,634
Other	27,432 (45.2)	60,698
Age quintiles		
16–19 years	140,737 (47.2)	298,637
20–21 years	71,336 (43.7)	163,185
22–24 years	75,534 (44.2)	170,971
25–29 years	73,115 (44.6)	163,808
30–69 years	78,337 (38.2)	204,945
Education		
At most high school	424,782 (44.0)	964,783
>High school	14,277 (38.8)	36,763
Marital status[a]		
Not married	288,850 (45.0)	642,156
Married	150,186 (41.8)	359,117
Pay grade		
Enlisted 1–3	257,257 (45.1)	570,769
Enlisted 4–6	119,031 (44.3)	268,759
Enlisted 7–9	14,537 (28.8)	50,439
Officers/warrant officers	48,234 (43.2)	111,579
Duration of service (quintiles)		
3 months to 2.7 years	35,805 (17.8)	201,002
2.8–4.0 years	104,477 (48.5)	215,647
4.1–7.3 years	98,080 (53.2)	184,358
7.4–14.9 years	109,662 (54.8)	200,254
>14.9 years	91,035 (45.5)	200,285
Stationed abroad		
Never	192,019 (33.1)	580,863
Ever	247,040 (58.7)	420,683
Stationed in Southwest Asia 6/98 or later		
No	429,821 (43.4)	991,347
Yes	9238 (90.6)	10,199
Stationed in S. Korea 12/98 or later		
No	306,212 (37.4)	818,420
Yes	132,847 (72.5)	183,126
Ever received hostile fire pay		
No	98,738 (19.1)	516,010
Yes	340,321 (70.1)	485,536
Career management field (CMF)		
Mechanical equipment repair	60,408 (50.4)	119,928
Support/admin	102,486 (46.3)	221,525
Craftsworkers	7476 (45.8)	16,339
Service/supply	48,056 (45.4)	105,947
Electrical equipment repair	34,412 (45.3)	75,920
Technical/allied specialties	12,033 (41.9)	28,734
Communications/intelligence	41,386 (40.6)	101,828
Infantry/gun crews	48,393 (40.2)	120,433
Officers	10,791 (39.0)	27,647
Healthcare	24,355 (35.3)	69,022
Major command		
Special operations	9119 (51.9)	17,573
8th US army	16,077 (49.1)	32,774
US army forces command	112,739 (46.3)	243,553
Training and doctrine	216,752 (45.6)	476,321
Fifth corps	21,727 (43.5)	49,916
Signal command	3412 (38.2)	8922
Other	33,481 (37.9)	88,252
US army Pacific	7306 (32.5)	22,457
Medical command	15,897 (32.2)	49,355
Intelligence and security	2502 (30.5)	8201
Recruiting command	21 (11.4)	184

[a] n = 273 missing marital status data.

(28.8%) compared to other pay grades (43–45%); those with shortest duration of service were least likely to be vaccinated (17.8% vs. 45.5–54.8%); and personnel ever stationed abroad were nearly twice as likely to have been vaccinated against anthrax compared to those never stationed abroad (58.7% vs. 33.1%). As expected from documented vaccination priorities, vaccination coverage was high among those stationed in Southwest Asia after June 1998 (90.6%) and on the Korean Peninsula after December 1998 (72.5%). Soldiers who had ever received hostile fire pay were nearly 4 times as likely to have been vaccinated (70.1% vs. 19.1%) compared with those who had not. Career management fields, which categorize military occupational specialty codes (i.e., jobs) into administrative groups, did not vary notably in vaccination history, except that individuals in officer groups and health care were less likely to have been vaccinated than others (39% and 35.3%, respectively, vs. 40.2–50.4%). An alternative categorization scheme, major command codes, show the highest proportions of soldiers vaccinated against anthrax were in special operations (51.9%), and the smallest proportions were in the recruiting command (11.4%). The mean and median duration of follow-up were higher for vaccinated soldiers (5.3 and 5.2 years, std. dev. 2.3 years) compared to unvaccinated soldiers (3.0 and 2.3 years, std. dev. 2.4 years; data not shown).

Just above five percent of included soldiers (5.2%; 52,151) were evaluated for disability (Table 3). Unadjusted rates show those receiving at least one dose of AVA were nearly 3 times less likely to have been evaluated for disability compared to unvaccinated personnel (177.7/100,000 vs. 60.4/100,000 person-months). Women were 1.8 times as likely as men to have been evaluated for disability (178.9 vs. 98.0/100,000 person-months), and white soldiers were evaluated for disability at higher rates than other race/ethnicity groups (117.4/100,000 vs. 82.9–104.8/100,000 person-months). The youngest and oldest soldiers had lower rates of disability evaluation (108.7 and 74.2/100,000 person-months, respectively) than soldiers in the middle categories of age (123.7–133/100,000 person-months). Education, pay grade and duration of service were inversely associated with disability evaluation. Those ever stationed abroad, receiving hostile fire pay, or stationed in Southwest Asia or on the Korean Peninsula after implementation of the anthrax vaccine policy were two to 4 times less likely to have been evaluated for disability than personnel not stationed in high-threat locations. Soldiers evaluated for disability averaged shorter duration of follow-up than those not evaluated: 2.9 years (std. dev. 2.0, median 2.5 years) vs. 4.1 years (std. dev. 2.6, median 3.5 years; data not shown).

3.1. *Predictors of disability evaluation (core model)*

Women were 83% (95% CI: 80%, 87%) more likely to be evaluated for disability than men (data not shown). In addition to gender, the core model predicting disability evaluation included receipt of hostile-fire pay and categories of race/ethnicity. Duration of service was a strong predictor of disability evaluation (inverse), but log–log plots showed violation of the proportional hazards assumption. We therefore stratified all subsequent analyses by decile of duration of service.

3.2. *Ever vs. never vaccinated*

We assessed the incremental effect of anthrax vaccination on the risk of disability evaluation associated with each term in the core model predicting disability (stratified by deciles of duration of service), and found little or no difference in risk associated with vaccination status, i.e., not exceeding 1%, in the value of the hazard ratio after adjusting for vaccination status. Because vaccination status is correlated with gender (Table 3), the lack of confounding indicated by the trivial percent change in hazard ratio suggests that vaccination status is not associated with risk of disability (Table 4). Partial log likelihood ratio tests indicated the vaccine indicator contributed statistically significantly to the model in three of the ten strata, those defined by the first decile of duration of

Table 3
Distribution of occupational/demographic factors by disability evaluation (ever/never) $n = 1{,}001{,}546$.

Occupational/demographic factor	Disability: count (%)	Total	Person-months	Crude rate/100,000 person-months
Anthrax-vaccinated				
No	35,619 (6.3)	562,487	20,046,580.9	177.7
Yes	16,532 (3.8)	439,059	27,372,856.1	60.4
Gender				
Male	39,628 (4.7)	838,391	40,417,932.1	98.0
Female	12,523 (7.7)	163,155	7,001,504.9	178.9
Race/ethnicity				
White	33,437 (5.4)	621,213	28,474,754.7	117.4
Black	12,404 (5.4)	229,001	11,831,597.7	104.8
Hispanic	3838 (4.2)	90,634	4,132,856.0	92.9
Other	2472 (4.1)	60,698	2,980,228.5	82.9
Age quintiles				
16–19 years	12,818 (4.3)	298,637	11,796,109.6	108.7
20–21 years	8800 (5.4)	163,185	6,615,191.1	133.0
22–24 years	10,319 (6.0)	170,971	7,819,307.0	132.0
25–29 years	11,214 (6.9)	163,808	9,066,863.4	123.7
30–69 years	9000 (4.4)	204,945	12,121,965.9	74.2
Education				
At most high school	50,445 (5.2)	964,783	45,388,814.6	111.1
>High school	1706 (4.6)	36,763	2,030,622.3	84.0
Marital status				
Not married	31,922 (5.0)	642,156	27,173,540.1	117.5
Married	20,227 (5.6)	359,117	20,238,869.7	99.9
Pay grade				
Enlisted 1–3	31,651 (5.6)	570,769	22,182,772.6	142.7
Enlisted 4–6	17,479 (6.5)	268,759	15,670,135.7	111.5
Enlisted 7–9	1000 (2.0)	50,439	2,494,124.7	40.1
Officers/warrant officers	2021 (1.8)	111,579	7,072,404.0	28.6
Duration of service quintiles				
3 months to 2.7 years	13,965 (7.0)	201,002	3,096,549.8	451.0
2.8–4.0 years	11,080 (5.1)	215,647	7,173,019.5	154.5
4.1–7.3 years	9731 (5.3)	184,358	9,150,768.3	106.3
7.4–14.9 years	13,091 (6.5)	200,254	13,995,915.2	93.5
>14.9 years	4284 (2.1)	200,285	14,003,184.1	30.6
Stationed abroad				
Never	34,115 (5.9)	580,863	21,915,891.0	155.7
Ever	18,036 (4.3)	420,683	25,503,545.9	70.7
Stationed in Southwest Asia 6/98 or later				
No	51,961 (5.2)	991,347	46,634,887.8	111.4
Yes	190 (1.9)	10,199	784,549.2	24.2
Stationed in S. Korea 12/98 or later				
No	45,849 (5.6)	818,420	35,706,700.6	128.4
Yes	6302 (3.4)	183,126	11,712,736.3	53.8
Ever received hostile fire pay				
No	37,927 (7.4)	516,010	17,817,750.4	212.9
Yes	14,224 (2.9)	485,536	29,601,686.6	48.1
CMF field				
Service/supply	7041 (6.7)	105,947	4,860,774.1	144.9
Healthcare	4478 (6.5)	69,022	3,250,376.4	137.8
Craftsworkers	1068 (6.5)	16,339	791,929.0	134.9
Officers	1332 (4.8)	27,647	1,007,832.3	132.2
Electrical equipment repair	4088 (5.4)	75,920	3,241,812.4	126.1
Mechanical equipment repair	7063 (5.9)	119,928	5,620,324.2	125.7
Communications/intelligence	5318 (5.2)	101,828	4,349,849.6	122.3
Support/admin	11,582 (5.2)	221,525	9,737,668.3	118.9
Infantry/gun crews	6665 (5.5)	120,433	5,989,239.2	111.3
Tech/allied specialties	1348 (4.7)	28,734	1,350,481.6	99.8
Major command				
Training and doctrine	25,640 (5.4)	476,321	19,246,188.6	133.2
US army forces command	14,175 (5.8)	243,553	12,691,454.2	111.7
US army Pacific	1319 (5.9)	22,457	1,255,592.6	105.1
Medical command	2611 (5.3)	49,355	2,524,352.6	103.4
Signal command	430 (4.8)	8922	457,341.5	94.0
Fifth corps	2670 (5.4)	49,916	2,843,072.3	93.9
8th US army	1590 (4.9)	32,774	1,743,825.9	91.2
Intelligence and security	321 (3.9)	8201	425,868.7	75.4
Special operations	747 (4.3)	17,573	1,043,990.0	71.6
Other	2622 (3.0)	88,252	5,144,062.0	51.0
Recruiting command	2 (1.1)	184	13,802.7	14.5

Table 4
Adjusted hazard ratios (HR) for females vs. males (n = 1,001,546), stratified by duration of service; effect of anthrax vaccination on risk of disability evaluation.

	Stratum estimate		Adjusted for race/ethnicity, HFP[a]		Race/ethnicity, HFP[a], vaccination		Change[b] (%)	95% CI[c]
	HR	95% CI	HR	95% CI	HR	95% CI		
Duration of service								
3 months to 1.4 years	1.94	1.85–2.04	1.81	1.72–1.90	1.80	1.72–1.90	−0.56	<0.0001
1.4– 2.4 years	1.74	1.65–1.82	1.48	1.41–1.56	1.48	1.41–1.56	0.00	0.15
2.4–3.1 years	2.10	1.98–2.24	1.89	1.77–2.02	1.89	1.78–2.02	0.00	0.46
3.1– 4 years	1.66	1.56–1.76	1.23	1.15–1.31	1.23	1.15–1.31	0.00	0.34
4–5.1 years	1.42	1.33–1.52	1.12	1.04–1.20	1.11	1.04–1.20	0.90	0.09
5.1–7 years	1.35	1.27–1.44	0.99	0.93–1.06	1.00	0.93–1.06	1.00	0.08
7–9.7 years	1.31	1.23–1.39	0.96	0.90–1.03	0.96	0.90–1.03	0.00	0.11
9.7–14.5 years	1.35	1.27–1.44	0.94	0.88–1.00	0.94	0.88–1.01	0.00	<0.0001
14.5–20.2 years	1.50	1.37–1.64	1.13	1.03–1.24	1.14	1.04–1.25	0.88	<0.0001
Over 20.2 years	1.37	1.17–1.60	1.08	0.92–1.26	1.08	0.92–1.27	0.00	0.33

[a] HFP: hostile fire pay indicator.
[b] Percent change in HR due to adjustment for vaccination status.
[c] p-value from the partial log likelihood ratio tests comparing the adjusted models without vaccination status to the adjusted models with vaccination status.

service (3 months to 1.4 years); the eighth decile of duration of service (9.7–14.5 year) and the ninth decile of duration of service (14.5–20.2 years).

Sixty-eight percent of all disabilities (35,487/52,151) were due to musculoskeletal problems, and we judged about 97% of these stemmed from traumatic injuries, based on clinical knowledge and familiarity with army medical coding (assessed by PJA). We repeated the analyses after excluding disabilities judged due to traumatic injuries and after limiting the analysis to soldiers with ≥4 years of follow-up after first vaccination dose (n = 92,412 with median = 6.5 person-years). These subsets yielded the largest incremental change in risk of disability associated with vaccination, −2.0% (partial log likelihood ratio test p-value < 0.0001) for non-traumatic injuries for soldiers in the seventh decile (7–9.7 years) of duration of service and −2.3% (p-value < 0.01) for non-traumatic permanent disability separation from the army for those in the sixth decile (5.1–7 years) of duration of service (data not shown).

Results were similar for all variations of the model we considered, in that addition of an indicator for vaccination status resulted in very small proportional changes in the estimated hazard ratios (0–4%), and the partial log likelihood ratio tests for the addition of the vaccine indicator were statistically significant in only a few of the 142 strata evaluated. Model variations are shown in Supplemental Table S2 (risks of any disability among race/ethnicity categories) and Supplemental Table S3 (risk of disability by category (i.e., permanent, temporary or discharge with and without severance) for men versus women).

There were too few cases in each category of reason for disability (i.e., physiological groups: musculoskeletal, neurological, respiratory, mental, digestive, cardiac, endocrine, other) to be analyzed by deciles of duration of service. Instead, we added age to the model, which is correlated with duration of service but does not violate the proportional hazards assumption as badly. Except for disabilities due to cardiac and endocrine problems, the risk of each category of reason for disability for women compared to men was, as expected, elevated; ORs range between 1.11 (neurological problems) and 1.59 (other disabilities). Although vaccination status was a statistically significant contributor to the model for nearly all types of disability, the percent change in risk with the addition of vaccination to the model ranged from less than 1% to 2.63%, again indicating trivial amounts of confounding (Supplemental Table S4). Because vaccination status is correlated with gender (Table 3), the negligible degree of confounding by vaccination status, indicated by the trivial percent change in hazard ratio, shows that vaccination is not associated with reason for disability (Supplemental Table S4).

3.3. Dose-response analysis

Although there was no overall effect of vaccination status on risk of disability evaluation, type of disability award, traumatic or non-traumatic reason for disability or reason for disability (i.e., physiological system), we investigated the possibility that different numbers of doses of AVA might be associated with differences in risk. Because duration of service was inversely associated with risk of disability evaluation and positively associated with numbers of doses of AVA, we categorized the vaccinated sub-cohort into mutually exclusive categories of duration of service, and compared the odds of disability for increasing numbers of vaccinations in each category compared to odds of disability for soldiers who remained unvaccinated during that category of duration of service. In one category, soldiers separating from the army with 2 years of service, there was a monotonic increase in risk of disability evaluation with increasing numbers of doses of AVA. Specifically, the OR for disability evaluation for soldiers with one dose of AVA was 0.41 (95% CI: 0.36, 0.47) compared to unvaccinated soldiers. For those receiving two doses, OR = 0.95 (95% CI: 0.84, 1.09), and OR = 3.51 (95% CI: 2.83, 4.35) for those receiving ≥5 doses of AVA compared to unvaccinated personnel (data not shown). After adjusting for gender, age, race/ethnicity and receipt of hostile fire pay, the OR for each dose increased in magnitude (Table 5). There was no gradient in risk for any other stratum, and most of the odds ratios were below 1.0.

No differences in occupational or demographic characteristics were evident for the apparently high-risk group of soldiers with 2 years of service, and there were no differences in reasons for disabilities granted (data not shown). More than 80% of soldiers with 2 years of service entered the army after 1999, however, and thus may have been engaged in the conflicts in Iraq and Afghanistan. Stratifying soldiers with 2 years of service by receipt of hostile fire pay again increased the apparent dose-response effect in this group. In contrast, 70% of soldiers with up to 1-year or more than 2 years of service entered the army before 2000. When we stratified the vaccinated sub-cohort by entry date before or after 2000, we observed a statistically significant inverse trend in risk with increasing numbers of doses for those joining before January 1, 2000. For those joining after January 1, 2000, risk of disability discharge was statistically significantly elevated for soldiers receiving any number of doses of AVA (Table 6).

4. Discussion

These analyses replicate observations reported previously [14], adding 3 years of observation and nearly 250,000 soldiers to the

Table 5
Adjusted[a] odds of disability evaluation for increasing numbers of doses compared to no doses of anthrax vaccine, stratified by years of service (n = 1,001,546).

Years of Service	Doses	OR	Lower CL	Upper CL
1	1 vs. 0	0.85	0.64	1.15
	2 vs. 0	1.11	0.76	1.62
	3 vs. 0	0.96	0.63	1.46
	4 vs. 0	0.82	0.19	3.43
	5 or more[b] vs. 0	1.10	0.14	8.84
2	1 vs. 0	0.68	0.60	0.78
	2 vs. 0	1.37	1.20	1.56
	3 vs. 0	2.10	1.90	2.33
	4 vs. 0	3.20	2.78	3.67
	5 or more[b] vs. 0	4.73	3.79	5.91
3	1 vs. 0	0.73	0.65	0.82
	2 vs. 0	0.82	0.72	0.92
	3 vs. 0	1.01	0.93	1.10
	4 vs. 0	1.22	1.12	1.33
	5 or more[b] vs. 0	1.43	1.31	1.57
4	1 vs. 0	1.07	0.93	1.23
	2 vs. 0	1.18	1.03	1.34
	3 vs. 0	1.23	1.11	1.35
	4 vs. 0	1.11	1.01	1.21
	5 or more[b] vs. 0	0.99	0.91	1.07
5	1 vs. 0	0.85	0.70	1.02
	2 vs. 0	0.97	0.81	1.56
	3 vs. 0	0.93	0.82	1.05
	4 vs. 0	0.82	0.73	0.92
	5 or more[b] vs. 0	0.82	0.74	0.91
6	1 vs. 0	0.83	0.72	0.97
	2 vs. 0	0.68	0.58	0.81
	3 vs. 0	0.87	0.78	0.97
	4 vs. 0	0.79	0.72	0.87
	5 or more[b] vs. 0	0.82	0.76	0.89
7 or more	1 vs. 0	0.81	0.73	0.90
	2 vs. 0	0.97	0.88	1.07
	3 vs. 0	0.97	0.90	1.04
	4 vs. 0	0.88	0.83	0.94
	5 or more[b] vs. 0	0.64	0.61	0.67

[a] Adjusted for gender, race/ethnicity, hostile fire pay.
[b] Category includes soldiers with 5–17 doses.

cohort, that demonstrated low overall risk of disability evaluation with no discernible patterns of increased or decreased risk of disability evaluation, separation from the army, type of or reason for disability associated with ever having been vaccinated against anthrax. Only among soldiers with 2 years of service who entered the army in 2000 or later was there a consistent, dose-related increase in odds of disability evaluation. In contrast, soldiers who enlisted before 2000 had a consistent, dose-related inverse trend in risk. There were no changes in the formulation, dosing schedule or mode of delivery of the AVA during the study period. The difference in the direction of the dose-response association based on calendar year of enlistment suggests a statistical artifact, probably related to likelihood of deployment, rather than a true, biological difference in risk associated with vaccine doses delivered.

Administrative data are demonstrably useful for research purposes, but can also be limited by a lack of detail or specific information, although army databases are likely to be more complete than many others. For example, the main study outcome, ever/never evaluated for disability, provides a surrogate for delayed onset or chronic health effects, rather than a direct measure of the outcome of interest. Soldiers are evaluated for disability when there is doubt about their ability to carry out the duties required by their rank and specialty. The size and duration of monetary awards granted is dependent on time in service, service-connectedness and severity of the disability, but there are mechanisms for granting severance to junior personnel. Among all vaccinated individuals, who nevertheless remained at low risk of the outcome, there was a consistent, but not statistically significant, elevation in risk of disability evaluation for each of the first 4 years following first AVA dose, and a declining trend for each year thereafter. This pattern seems to coincide with career path through the army, and is consistent with the lower rate of disability evaluation noted for those vaccinees with longer duration of service and higher pay grade (i.e., career army personnel), as well as the increases in risk noted for those with 2 years of service. Soldiers may be motivated to seek disability evaluation, and associated financial benefits, shortly before the planned conclusion of their army careers.

We consider it likely that residual confounding by factors simultaneously associated with vaccination and separation from the army dominate over any direct vaccine effect. Evidence for such confounding is provided by: (a) the policy in effect during the study period that required vaccination for all personnel deploying to the Middle East, Southwest Asia, the Horn of Africa and the Korean Peninsula; (b) the disproportionate representation of unvaccinated personnel (6.3%) compared to vaccinated personnel (3.8%) among the small subgroup ever evaluated for disability; and (c) the opposite dose-response effects for soldiers with 2 years of service who joined the army before or after 2000. It is likely that deployed personnel have greater levels of baseline physical fitness than non-deployed persons, and may be less injury prone or better able to recover from injuries [25]. We suspect this "Healthy Warrior Effect" [26] explains the lower risks of disability experienced by vaccinated compared to unvaccinated personnel for those soldiers who enlisted prior to 2000. The available data could not be used to limit the study population to those eligible for vaccination, which would have been the most valid subset of the population for these analyses. As more complete and valid records of deployments become available for inclusion in the TAIHOD, it may be feasible to design more focused analyses and reduce selection bias.

This analysis did not consider the potential effects of multiple vaccinations on risk of disability. Vaccinations in the military are typically against several organisms, including both anthrax and smallpox. Because multiple vaccinations are routinely delivered to deploying personnel, analysis of one is effectively an analysis of all.

Our findings, based on multiple stratified analyses and various definitions of disability outcome, are consistent with results of other studies that generally show AVA to be safe. For example,

Table 6
Adjusted[a] odds ratios by date of entering army (before or after January 1, 2000), among vaccinated (n = 439,059).

Adjusted[a] OR's for Doses	Entered army	
	<January 1, 2000	≥January 1, 2000
2 vs. 1	1.08 (0.98–1.20)	1.36 (1.23–1.50)
3 vs. 1	1.08 (0.99–1.18)	1.65 (1.51–1.81)
4 vs. 1	0.97 (0.89–1.05)	1.71 (1.56–1.87)
5 or more vs. 1[b]	0.80 (0.74–0.87)	1.33 (1.21–1.46)
p-Value for trend (direction)	<0.0001 (−)	<0.0001 (+)

[a] Adjusted for gender, race/ethnicity, paygrade, and hostile fire pay.
[b] Category includes soldiers with 5–17 doses.

others have shown that short-term risks associated with AVA are similar to risks reported for other adult vaccines, with about 35% of vaccinated individuals experiencing acute local effects characterized as "mild" to "moderate" intensity (e.g., soreness, itching or swelling at the injection site) and less than 8% experiencing moderate to severe local effects or systemic effects requiring medical attention or time off from work [15–17]. Hospitalization rates and functional status were found to be similar for nearly 68,000 vaccinated and unvaccinated Millennium Cohort Study participants [18]. While it is possible that AVA may be causally associated with some disability separations from the army, this must be a rare situation, or such events would have been detected by the comprehensive analysis reported here.

Acknowledgments

The authors are indebted to COL (Ret) John Grabenstein for reading drafts of this manuscript and providing context for the interpretation of the data. Neither the original study nor this follow-up would have been undertaken without his vision. We are also grateful to Mr. Jeffrey Williams and Ms. Lauren Komp for producing the analytical data sets and their able management of the TAIHOD.

Funding: Funding for this work was provided by the US Department of the Army, contract number W911QY-06-P-0337.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.06.028.

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